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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,058	05/08/2001	Kenneth C. Parker	SYP-172	2910

7590 09/23/2004

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,058	PARKER ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed 10 March 2004 is acknowledged. In the amendment filed therein the specification along with claims 1, 13, 16, 18, and 21 have been modified.

2. Currently claims 1-22 are pending and currently under consideration.

REJECTIONS WITHDRAWN

Specification

3. Applicant's have amended the Abstract to eliminate cited new matter, therein obviating the rejection. Accordingly the rejection is withdrawn.

Claim Rejections - 35 USC § 112

4. Claims 1-22 are rejected withdrawn from rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) have been amended to eliminate non-supported (disclosed in the specification) subject matter. The rejection is withdrawn.

5. Claims 1-22 are withdrawn from rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have corrected the deficiencies by amendment or convincing arguments. Accordingly the rejection is withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1-3, 6-9, and 10-21 are rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807).

Aebersold et al. teach methods of analyzing proteins or protein function in complex mixtures. The method utilizes labeling compositions comprising the formula A-L-PRG. Wherein A represents an affinity label, PRG is a protein reactive group, and L is a linker group. This same formula is taught in the instant disclosure on page 8.

The PRG selectively reacts with certain groups that are typically found in peptides (sulfhydryl, amino, carboxy, homoserine lactone groups). One or more affinity labeled reagents with different PRG groups is introduced into a mixture containing proteins. After protein A-L-PRG mixing the digestion is optional. The PRG complex binds with the proteins of interest to produce a measurable tagged binding entity. This entity can subsequently be evaluated/analyzed via liquid chromatography/mass spectrometry (LC/MS). See abstract and page 8.

The method can be employed to screen and identify proteins, which are differential expressed in cells, tissue, or biological fluids. It is further possible to determine the absolute amount of the proteins utilizing known amounts of internal standards. See page 9 1st paragraph. The process is applicable in determining the state of protein modification, enzyme activity, and function. See pages 9-11.

Aebersold et al. differ from the instant invention in not specifically including a protein separation step involving electrophoresis (claim 1 step (e)), transblotting and digestion (claim 9) in their protein identification method.

However, Bienvenut et al. disclose methods of combining transblotting (OSDT), gel digestion of all proteins in parallel (PIGD) applied to electrophoresis techniques to increase the throughput of protein identification and characterization in proteome studies.

The procedures included 1-DE and 2-DE gel electrophoresis. See page 4804. Peptides liberated during transblotting of proteins through an immobilized trypsin membrane were trapped on a PVDF membrane and identified by mass spectrometry. See abstract and pages 4801-4803.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the OSDT, PIG, electrophoresis combination procedure of Bienvenut et al. in the protein identification method of Aebersold et al. because Bienvenut et al. taught that the combination "led to greatly improved digestion of high molecular weight and basic proteins without loss of low molecular weight polypeptides. See abstract.

One of ordinary skill in the art would have been motivated to employ the combination procedure of Bienvenut et al. to take advantage of an automated integrated system involving MALDI-TOF MS scanning, spectra treatment, protein identification, in order to generate a fully annotated 2-DE map for protein identification. See page 4807.

II. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) and in further view of Yates et al. (US Patent #5,538,897).

Please see Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) as set forth above.

Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) differ from the instant invention in not specifically teaching protein/peptide sequence via tandem mass spectrometry.

However, Yates et al. disclose a method of correlating a peptide fragment with amino acid sequences derived from a database. A peptide is analyzed by a tandem mass spectrometer to yield a peptide fragment mass spectrum (mass fingerprinting).

A protein sequence database or a nucleotide sequence database is used to predict/identify the fragment. For each candidate sequence, a plurality (pool) of fragments of the sequences is identified and the masses-m/z ratios of the fragments are predicted and used to form a predicted mass spectrum. See abstract.

Aebersold et al. in view of Bienvenut et al. and Yates et al. are all analogous art because they are from the same field of endeavor; all three inventions teach methods involving protein fragment characterization and identification.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize tandem mass spectrometry database sequence comparison as taught by Yates et al. to identify the fragments found in the method of Aebersold et al. in view of Bienvenut et al. to evaluate a pool of modified protein sequences, because Yates et al. taught that the patented system for correlating fragment spectra with known sequences would avoid delay and/or subjectivity in hypothesizing or deducing candidate amino acid sequences from the fragment spectra. (Column 1 lines 44-62).

One having ordinary skill in the art would have been motivated to do this because in order to achieve maximal data processing/protein manipulation to determine the parameter of interest.

III. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) and in further view of Clauser et al. (Proceedings of the National Academy of Sciences, USA, 1995, 92(11), 5072-6).

See Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) as set forth above.

Aebersold et al. in view of Bienvenut et al. differ from the instant invention in not specifically teaching post-translational modification status of a protein/peptide by gel analysis.

However, Clauser et al. disclose a method involving mass spectrometry and two-dimensional polyacrylamide gel electrophoresis for the rapid identification and characterization of proteins. The method can detect and structurally characterize covalent modifications. The authors have characterized several post-translational modification and chemical modifications that may result from electrophoresis or subsequent sampling processing steps. The detection of these modifications is required in order to reliably and unambiguously establish the identify of each protein. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure post-translational protein modification as taught by Clauser et al. in the method of Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) because Clauser et al. taught that the method allowed for the study cell-type dependent gene expression and large suites of cellular proteins with unprecedented speed and rigor. See abstract and page 5076.

IV. Claims 1-8 and 10-21 are rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999).

Aebersold et al. teach methods of analyzing proteins or protein function in complex mixtures. The method utilizes a labeling compositions comprising the formula A-L-PRG. Wherein A represents an affinity label, PRG is a protein reactive group, and L is a linker group. This same formula is taught in the instant disclosure on page 8. The PRG selectively reacts with certain groups that are typically found in peptides (sulfhydryl, amino, carboxy, homoserine lactone groups). One or more affinity labeled reagents with different PRG groups is introduced into a mixture containing proteins. After protein A-L-PRG mixing the digestion is optional. The PRG complex binds with the proteins of interest to produce a measurable tagged binding entity. This entity can subsequently be evaluated/analyzed via liquid chromatography/mass spectrometry (LC/MS). See abstract and page 8.

The method can be employed to screen and identify proteins, which are differential expressed in cells, tissue, or biological fluids. It is further possible to determine the absolute amount of the proteins utilizing known amounts of internal standards. See page 9 1st paragraph. The process is applicable in determining the state of protein modification, enzyme activity, and function. See pages 9-11.

Aebersold et al. differ from the instant invention in not specifically including a protein separation step involving gel electrophoresis in their method.

However, Gygi et al. disclose methods for quantitative protein analysis. The method combines protein separation (two dimensional polyacrylamide gel electrophoresis-2D-PAGE) with mass spectrometry (MS) or tandem mass spectrometry (MS/MS). See page 994, 1st column, 2nd paragraph and page 998 2nd column last paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize electrophoresis separation along with MS or MS/MS as taught by Gygi et al. to identify the protein and or protein fragments found in the method of Aebersold et al., because Gygi et al. taught that their method allowed for large scale analysis of not only highly abundant proteins in cell lysates but could detect very-low abundance proteins as well. See page 998, 2nd column last paragraph.

Therefore one of ordinary skill in the art would have been motivated to include protein separation via electrophoresis and the mass spectrometry analysis procedure in order to acquire rapid and precise evaluation of all proteins (high and low) within a sample.

V. Claim 9 is rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) and in further of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807).

Please see Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) as set forth above.

Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) differ from the instant invention in failing to teach transblotting and digestion combinations in protein identification.

Bienvenut et al. disclose methods of combining transblotting (OSDT) and in gel digestion of all proteins in parallel (PIGD) to increase the throughput of protein identification and characterization in proteome studies. Peptides liberated during transblotting of proteins through an immobilized trypsin membrane were trapped on a PVDF membrane and identified by mass spectrometry. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the OSDT/PIG combination procedure of Bienvenut et al. in the protein identification method of Aebersold et al. in view of Gygi et al., because Bienvenut et al. taught that the combination "led to greatly improved digestion of high molecular weight and basic proteins without loss of low molecular weight polypeptides. See abstract.

One of ordinary skill in the art would have been motivated to employ the combination procedure of Bienvenut et al. to take advantageous of an automated integrated system involving MALDI-TOF MS scanning, spectra treatment, protein identification, in order to generate a fully annotated 2-DE map. See page 4807.

VI. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) and in further view of Clauser et al. (Proceedings of the National Academy of Sciences, USA, 1995, 92(11), 5072-6).

See Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) as set forth above.

Aebersold et al. in view of Gygi et al. differ from the instant invention in not specifically teaching post-translational modification status of a protein/peptide by gel analysis.

However, Clauser et al. disclose a method involving mass spectrometry and two-dimensional polyacrylamide gel electrophoresis for the rapid identification and characterization of proteins. The method can detect and structurally characterize covalent modifications. The authors have characterized several post-translational modification and chemical modifications that may result from electrophoresis or subsequent sampling processing steps. The detection of these modifications is required in order to reliably and unambiguously establish the identify of each protein. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure post-translational protein modification as taught by Clauser et al. in the method of Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) because Clauser et al. taught that the method allowed for the study cell-type dependent gene expression and large suites of cellular proteins with unprecedented speed and rigor. See abstract and page 5076.

Response to Arguments

Applicant contend that the combination of Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) do not teach protein electrophoresis or separation prior to digestion. This argument was carefully considered but not found persuasive because Bienvenut et al. teach simultaneous electrophoresis and digestion as well as electrophoresis before digestion.

Specifically, these teaching are found in Bienvenut et al. on page 4801 1st column 1st paragraph, starting at line 3 (simultaneous digestion). On page 4802 1st column 3rd paragraph, the OSDT process involves SDS-PAGE (electrophoresis) protein separation followed by Electrotransfer then digestion. On page 4802 1st column 4th paragraph through 2nd column 1st paragraph, the PIGD process describes a technique wherein immediately after SDS-PAGE protein separation the gels are partially digested and then completely digested. All the processed samples are read in a mass spectrometer system for final evaluation. See page 4802 2nd column 3rd paragraph.

Applicant also contends that the combination of Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) does not teach the instant invention because they do not teach methods wherein electrophoresis is conducted prior to detection by mass spectrometry. This argument was carefully considered but not found persuasive because Gygi et al. disclose the utility of electrophoresis in combination with mass spectrometry analysis. For example see page 994 1st column 2nd paragraph and page 998 2nd column 2nd paragraph lines 1-6. It is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to a person of ordinary skill in the art. *In re Boe*, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966).

Further, it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. *Ex parte Rubin*, 128 USPQ 440 (POBA 1959) Cohn v. Comr. Patents, 251 F.Supp.437, 148 USPQ 486 (DC 1966).

Applicant's arguments with respect to the dependent claims were directed to the combination of Aebersold et al. in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) or Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999), the rejection has been addressed above. Accordingly the rejections are maintained.

7. For reasons aforementioned, no claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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